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Getting the diagnosis right: beyond El Escorial

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Abstract The development and endorsement of the 'El Escorial criteria' by the World Federation of Neurology (WFN) for the diagnosis of amyotrophic lateral sclerosis (ALS) in 1990 and subsequent revision of these guidelines in April 1998 has provided physicians with a much needed tool in the secure diagnosis of ALS. However, even today, over 100 years since ALS was first described by Charcot, when asked to define ALS most neurologists will answer that ALS remains an extremely difficult disease to diagnose early and therefore to manage optimally. Despite the WFN's admirable commitment to optimising the management of ALS the definition of the early stages of ALS is still not clear. To appreciate why this remains so, the development of our understanding of ALS as documented by case reports in the literature will be discussed in this paper.

Key words Amyotrophic lateral sclerosis · Charcot · El Escorial criteria · Clinicopathological disease spectrum

Introduction

At the end of May 1990, clinicians and scientists worldwide met together to try to define precise diagnostic criteria which could be applied to further studies concerning patients with amyotrophic lateral sclerosis (ALS). This, the El Escorial meeting, was the first international attempt to define practical guidelines for the diagnosis of ALS. The output was a set of criteria which clinically defined ALS as a progressive primary degeneration of upper and lower motor neurons (UMNs and LMNs) in the absence of other disease processes. It also categorized ALS into *suspected*, *possible*, *probable* and *definite* subdivisions and attempted to distinguish ALS-related syndromes and ALS variants [2]. In the light of recent developments in the genetics and molecular biology of ALS, the WFN organized another workshop in 1998 to discuss their existing guidelines for the design and execution of clinical trials in ALS and to revisit their widely accepted El Escorial criteria for the diagnosis of ALS. However, despite these recent activities the definition of ALS as a disease or as a syndrome is still not definitely clear. For example the WFN clinical definition of ALS is open to question when 'other disease processes' such as progressive muscular atrophy, primary lateral sclerosis (PLS) and ALS variants (extrapyramidal signs, cerebellar degeneration and dementia) are taken into context.

Historical view of ALS

To go beyond the El Escorial criteria, it is worth exploring the history of ALS. The first page of this story was written in 1865 by Charcot in a case report of a hysterical woman with a permanent 'contracture' of limbs [3]. Postmortem examination demonstrated 'fascicular' sclerosis of the lateral tract of the medulla. This was the first description of involvement of the lateral tract of the medulla and the first attempt to associate a clinical symptom, the 'contracture', with this lesion.

The following decade was the scene of vigorous debates which led to the recognition of motor neurons as the target of the 'paralysie musculaire atrophiante' (Cruveil-

hier, 1852) and to the formalization of three nosological concepts: progressive muscular atropy (PMA), PLS and ALS (Charcot's disease) [7]. The three main criteria selected by Charcot (1874) to characterize ALS were motor weakness of rapid onset, without clear relation to atrophy; a permanent 'contracture'; spontaneous muscular pain triggered by pressure or traction [4]. He recognized a typical pattern: a disease onset in the hand, with prominent contracture in the legs and, often, bulbar involvement. Charcot established a relationship between motor neurons and muscle atrophy, and between the lateral tract and the 'contracture', but this statement did not imply spasticity and the pyramidal tract. This link was made by Raymond who established the concept of a bipolar disease with UMN and LMN involvement: in other words, a motor syndrome with a clinical syndrome made up of the association of symptoms and signs related to involvement of both UMNs and LMNs [9].

However, several neuropathological reports in the literature in the late 19th century [1, 3, 5, 6, 7] suggested that many anatomical structures are involved in ALS, including: basal ganglia, spinocerebellar pathways, vestibular nuclei, reticular nuclei and interneurons. The extent and nature of the pyramidal tract involvement was also a matter of discussion. Recently, Ince and colleagues at the Department of Neuropathology, Newcastle General Hospital, UK [8] suggested considering ALS, PMA, PLS, ALS-dementia, frontal lobe dementia, cerebellar degeneration as syndromic manifestations of a similar pathogenetic cascade. Ince and colleagues reported that while the El Escorial criteria were intended for research purposes, use of these criteria for entry into clinical trials may result in the exclusion of some patient groups with related disorders that are likely to share etiological mechanisms but which are not classified as '*definite* ALS' or '*probable* ALS'. For example, new evidence regarding the central role of oxidative stress and abnormal glutamatergic neurotransmission in familial and sporadic ALS seem applicable across all these disorders. Moreover, new evidence regarding the molecular pathology of inclusion bodies in these various syndromes (ubiquitin and hyaline conglomerate inclusions) shows striking similarities between them. However, marked differences in the anatomical distribution of lesions determine the predominance and type of motor and cognitive features in each syndrome, highlighting the concept that a clinicopathological spectrum is relevant to ALS and other late onset neurodegenerative disorders including multisystem atrophies, the Lewy body disorders and various manifestations of Alzheimer's disease.

What is ALS clinically?

So how should the neurologist, therefore, view ALS clinically? A number of questions come to mind in this view:

- Are we facing the same situation as for Parkinson's disease and Parkinsonism?
- Is there a central core of ALS, i.e. ALS disease?
- And how is it possible to distinguish ALS from 'ALSism', e.g. on clinical, pathological, pharmacological, physiopathological and/or pathogenic data?

Based on clinical data, is ALS disease the schematic bipolar (UMN and LMN) syndrome? Have we in fact chosen the correct fundamentals to answer this question? I feel that this scheme could be restricting our understanding of a more complete and bigger picture, in the sense that we commonly confine most of the clinical signs and symptoms to this bipolar model. A key question which comes to mind when considering pathological data is, are we really taking into account the real nature of some of Charcot's characteristic features of the disease such as 'contracture', weakness, muscle pain (this symptom has now fallen into abeyance). Because we are still faced with so many unknowns regarding ALS, perhaps we have simply missed the most important clinical tools which would allow the separation of ALS from ALSism? Other clinical features such as site and mode of onset and rate of disease progression, may also feature significantly in this respect.

Conclusions

I believe that in getting the diagnosis right we must go beyond El Escorial. The concept of a clinicopathological spectrum will certainly gain increasing importance (as noted by Ince and colleagues) as therapies evolve from the symptomatic to those directed at underlying pathogenic events. To this end, we look forward to progress in the areas of new therapeutic interventions and molecular pathogenesis which will enable some of these questions to be answered more consistently.

References

1. Bertrand I, Van Bogaert L (1925) Rapport sur la sclérose latérale amyotrophique. (Anatomie pathologique) Rev Neurol I:779–806

2. Brooks B (1994) El Escorial World Federation of Neurology criteria for the diagnosis of amotrophic lateral sclerosis. Subcommittee on Motor Neuron Diseases/Amyotrophic Lateral Sclerosis of the World Federation of Neurology Research Group on Neuromuscular Diseases and the El Escorial 'Clinical limits of amyotrophic lateral sclerosis' workshop contributors. J Neurol Sci 124:96–107

3. Charcot M (1865) Sclérose des cordons lateraux de la moelle épinière, chez une femme hystérique, atteinte de contracture permanente des quatre membres. Union Medicale; 25: 451–472
4. Charcot M (1874) De la sclerose lateràle amyotrophique. Progrès Medicale 2:325–340:341–356: 453–485
5. Charcot M (1874) Contribution à l'étude de l'atrophie musculaire progressive de type Aran-Duchenne. Thèse, Paris
6. Charcot M, Joffrey A (1869) Deux cas d'atrophie musculaire progressive avec lesions de la substance grise et desfarsilaux anterior-latéraux de la moelle épinière. Archives Physiologie Normale et Pathologié 2:354–367:629–649:744–760
7. Cruveilhier J (1853) Sur la paralysie musclaire progressive atrophique. Arch Gen Med 91:561–603
8. Ince PG, Lowe J, Shaw PJ (1998) Amyotrophic lateral sclerosis: current issues in classification, pathogenesis and molecular pathology. Neuropathol Appl Neurobiol 24:104–117
9. Raymond F (1898) Legons sur les maladies du systéme nerveux. Doin ed Paris 468–506